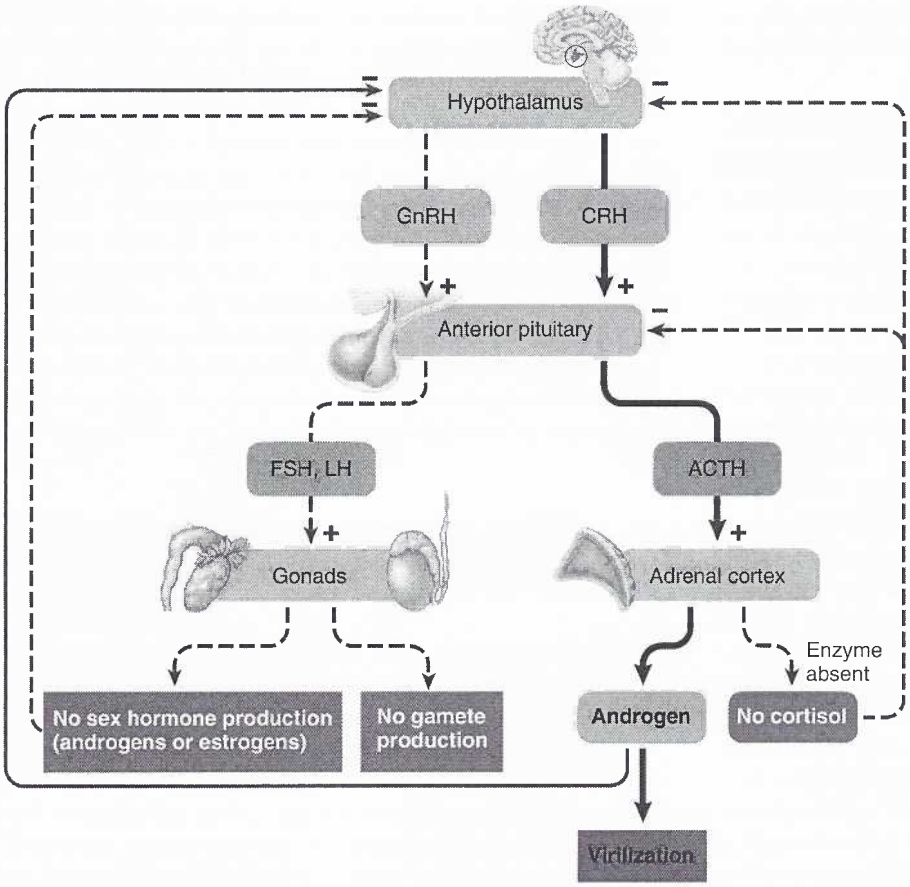


● **FIGURE 19-11 Hormonal interrelationships in adrenogenital syndrome.** The adrenocortical cells that are supposed to produce cortisol produce androgens instead because of a deficiency of a specific enzyme essential for cortisol synthesis. Because no cortisol is secreted to act in negative-feedback fashion, CRH and ACTH levels are elevated. The adrenal cortex responds to increased ACTH by further increasing androgen secretion. The excess androgen produces virilization and inhibits the gonadotropin pathway, with the result that the gonads stop producing sex hormones and gametes.

latter reduces ECF volume, including circulating blood volume, which in turn lowers blood pressure (hypotension).

Symptoms of cortisol deficiency are as would be expected: poor response to stress, hypoglycemia (low blood glucose) caused by reduced gluconeogenic activity, and lack of permissive action for many metabolic activities. The primary form of the disease also produces hyperpigmentation (darkening of the skin) resulting from excessive secretion of ACTH. Because the pituitary is normal, the decline in cortisol secretion brings about an uninhibited elevation in ACTH output (resulting from reduced negative feedback). Recall that ACTH and α melanocyte-stimulating hormone (α-MSH, a skin-darkening hormone that promotes dispersion of the pigment melanin) can both be cleaved from the same pro-opiomelanocortin precursor molecule (but not at the same time nor in the same organ; see p. 672). However, being closely related, at high levels ACTH can also bind with α-MSH's receptors in the skin and cause darkening of the skin.

Having completed discussion of the adrenal cortex, we now shift attention to the adrenal medulla.

The adrenal medulla consists of modified sympathetic postganglionic neurons

The adrenal medulla is actually a modified part of the sympathetic nervous system. A sympathetic pathway consists of two neurons in sequence—a preganglionic neuron originating in the CNS, whose axonal fiber terminates on a second peripherally located postganglionic neuron, which in turn terminates on the effector organ (see p. 238). The neurotransmitter released by sympathetic postganglionic fibers is norepinephrine, which interacts locally with the innervated organ by binding with specific target receptors known as *adrenergic receptors.*

The adrenal medulla consists of modified postganglionic sympathetic neurons called **chromaffin cells** because of their staining preference for chromium ions. Unlike ordinary postganglionic sympathetic neurons, chromaffin cells do not have axonal fibers that terminate on effector organs. Instead, on stimulation by the preganglionic fiber the chromaffin cells release their chemical transmitter directly into the circulation (see ● Figure 7-2, p. 239). In this case, the transmitter qualifies as a hormone instead of a neurotransmitter. Like sympathetic fibers, the adrenal medulla does release norepinephrine, but its most abundant secretory output is a similar chemical messenger known as **epinephrine.** Both epinephrine and norepinephrine belong to the chemical class of catecholamines, which are derived from the amino acid tyrosine (see p. 661). Epinephrine and norepinephrine are the same except that epinephrine also has a methyl group.

STORAGE OF CATECHOLAMINES IN CHROMAFFIN GRANULES Catecholamine is synthesized almost entirely within the cytosol of the adrenomedullary secretory cells. Once produced, epinephrine and norepinephrine are stored in **chromaffin granules,** which are similar to the transmitter storage vesicles found in sympathetic nerve endings. Segregation of catecholamines in chromaffin granules protects them from being destroyed by cytosolic enzymes during storage.

SECRETION OF CATECHOLAMINES FROM THE ADRENAL MEDULLA Catecholamines are secreted into the blood by exo-

cytosis of chromaffin granules. Their release is analogous to the release mechanism for secretory vesicles that contain stored peptide hormones or the release of norepinephrine at sympathetic postganglionic terminals.

Of the total adrenomedullary catecholamine output, epinephrine accounts for 80% and norepinephrine for 20%. Whereas epinephrine is produced exclusively by the adrenal medulla, the bulk of norepinephrine is produced by sympathetic postganglionic fibers. Adrenomedullary norepinephrine is generally secreted in quantities too small to exert significant effects on target cells. Therefore, for practical purposes we can assume that norepinephrine effects are predominantly mediated directly by the sympathetic nervous system and that epinephrine effects are brought about exclusively by the adrenal medulla.

Epinephrine and norepinephrine vary in their affinities for the different adrenergic receptor types.

Epinephrine and norepinephrine have differing affinities for four distinctive receptor types: α_1, α_2, β_1, and β_2 adrenergic receptors (see p. 243) (see ▲ Tables 7-3 and 7-4 to review the distribution of these receptor types among target organs).

Norepinephrine binds predominantly with α and β_1 receptors located near postganglionic sympathetic-fiber terminals. Hormonal epinephrine, which can reach all α and β_1 receptors via its circulatory distribution, interacts with these same receptors. Norepinephrine has a little greater affinity than epinephrine for the α receptors, and the two hormones have approximately the same potency at the β_1 receptors. Thus, epinephrine and norepinephrine exert similar effects in many tissues, with epinephrine generally reinforcing sympathetic nervous activity. In addition, epinephrine activates β_2 receptors, over which the sympathetic nervous system exerts little influence. Many of the essentially epinephrine-exclusive β_2 receptors are located at tissues not even supplied by the sympathetic nervous system but reached by epinephrine through the blood. Examples include skeletal muscle, where epinephrine exerts metabolic effects such as promoting the breakdown of stored glycogen, and bronchiolar smooth muscle, where it causes bronchodilation.

Sometimes epinephrine, through its exclusive β_2-receptor activation, brings about a different action from that elicited by norepinephrine and epinephrine action through their mutual activation of other adrenergic receptors. As an example, norepinephrine and epinephrine bring about a generalized vasoconstrictor effect mediated by α_1-receptor stimulation. By contrast, epinephrine promotes vasodilation of the blood vessels that supply skeletal muscles and the heart through β_2-receptor activation (see p. 359).

Realize, however, that epinephrine functions only at the bidding of the sympathetic nervous system, which is solely responsible for stimulating its secretion from the adrenal medulla. Epinephrine secretion always accompanies a generalized sympathetic nervous system discharge, so sympathetic activity indirectly controls actions of epinephrine. By having the more versatile circulating epinephrine at its call, the sympathetic nervous system has a means of reinforcing its own neurotransmitter effects plus a way of executing additional actions on tissues that it does not directly innervate.

Epinephrine reinforces the sympathetic nervous system and exerts additional metabolic effects.

Adrenomedullary hormones are not essential for life, but virtually all organs in the body are affected by these catecholamines. They play important roles in mounting stress responses, regulating arterial blood pressure, and controlling fuel metabolism. The following sections discuss epinephrine's major effects, which it achieves either in collaboration with the sympathetic transmitter norepinephrine or alone to complement direct sympathetic response.

EFFECTS ON ORGAN SYSTEMS Together, the sympathetic nervous system and adrenomedullary epinephrine mobilize the body's resources to support peak physical exertion in emergency or stressful situations. The sympathetic and epinephrine actions constitute a fight-or-flight response that prepares the person to combat an enemy or flee from danger (see p. 240). Specifically, the sympathetic system and epinephrine increase the rate and strength of cardiac contraction, increasing cardiac output, and their generalized vasoconstrictor effects increase total peripheral resistance. Together, these effects raise arterial blood pressure, thus ensuring an appropriate driving pressure to force blood to the organs most vital for meeting the emergency. Meanwhile, vasodilation of coronary and skeletal muscle blood vessels induced by epinephrine and local metabolic factors shifts blood to the heart and skeletal muscles from other vasoconstricted regions of the body.

Because of their profound influence on the heart and blood vessels, the sympathetic system and epinephrine also play an important role in the ongoing maintenance of arterial blood pressure.

Epinephrine (but not norepinephrine) dilates the respiratory airways to reduce the resistance encountered in moving air in and out of the lungs. Epinephrine and norepinephrine also reduce digestive activity and inhibit bladder emptying, both activities that can be "put on hold" during a fight-or-flight situation.

METABOLIC EFFECTS Epinephrine exerts some important metabolic effects. In general, epinephrine prompts the mobilization of stored carbohydrate and fat to provide immediately available energy for use as needed to fuel muscular work. Specifically, epinephrine increases the blood glucose level by several different mechanisms. First, it stimulates both hepatic (liver) gluconeogenesis and **glycogenolysis,** the latter being the breakdown of stored glycogen into glucose, which is released into the blood. Epinephrine also stimulates glycogenolysis in skeletal muscles. Because of the difference in enzyme content between liver and muscle, however, muscle glycogen cannot be converted directly to glucose. Instead, the breakdown of muscle glycogen releases lactate into the blood. The liver removes lactate from the blood and converts it into glucose, so epinephrine's actions on skeletal muscle indirectly help raise blood glucose levels. Epinephrine and the sympathetic system may further add to this hyperglycemic effect by inhibiting the secre-

tion of insulin, the pancreatic hormone primarily responsible for removing glucose from the blood, and by stimulating glucagon, another pancreatic hormone that promotes hepatic glycogenolysis and gluconeogenesis. In addition to increasing blood glucose levels, epinephrine also increases the level of blood fatty acids by promoting lipolysis.

Epinephrine's metabolic effects are appropriate for fight-or-flight situations. The elevated levels of glucose and fatty acids provide additional fuel to power the muscular movement required by the situation and also assure adequate nourishment for the brain during the crisis when no new nutrients are being consumed. Muscles can use fatty acids for energy production, but the brain cannot.

Because of its other widespread actions, epinephrine also increases the overall metabolic rate. Under the influence of epinephrine, many tissues metabolize faster. For example, the work of the heart and respiratory muscles increases, and the pace of liver metabolism steps up. Thus, epinephrine as well as thyroid hormone can increase the metabolic rate.

OTHER EFFECTS Epinephrine affects the central nervous system to promote a state of arousal and increased CNS alertness. This permits "quick thinking" to help cope with the impending emergency. Many drugs used as stimulants or sedatives exert their effects by altering catecholamine levels in the CNS.

Both epinephrine and norepinephrine cause sweating, which helps the body rid itself of extra heat generated by increased muscular activity. Also, epinephrine acts on smooth muscles within the eyes to dilate the pupil and flatten the lens. These actions adjust the eyes for more encompassing vision so that the whole threatening scene can be quickly viewed.

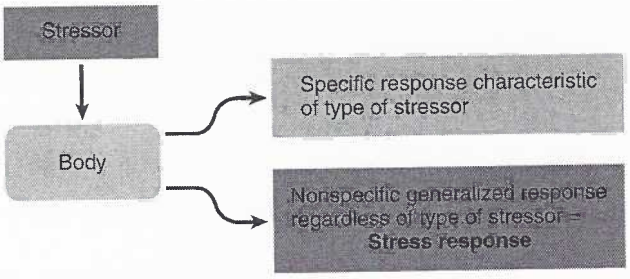
Sympathetic stimulation of the adrenal medulla is solely responsible for epinephrine release.

Catecholamine secretion by the adrenal medulla is controlled entirely by sympathetic input to the gland. When the sympathetic system is activated under conditions of fear or stress, it simultaneously triggers a surge of adrenomedullary catecholamine release. The concentration of epinephrine in the blood may increase up to 300 times normal, with the amount of epinephrine released depending on the type and intensity of the stressful stimulus.

Because both components of the adrenal gland play an extensive role in responding to stress, this is an appropriate place to pull together the major factors involved in the stress response.

Integrated Stress Response

Stress is the generalized, nonspecific response of the body to any factor that overwhelms, or threatens to overwhelm, the body's compensatory abilities to maintain homeostasis. Contrary to popular usage, the agent inducing the response is correctly called a *stressor,* whereas *stress* refers to the state induced by the stressor. The following types of noxious stimuli illustrate the range of factors that can induce a stress response: *physical* (trauma, surgery, intense heat or cold); *chemical* (reduced O_2 supply, acid–base imbalance); *physiologic* (heavy exercise, hemorrhagic shock, pain); *infectious* (bacterial invasion); *psychological* or *emotional* (anxiety, fear, sorrow); and *social* (personal conflicts, change in lifestyle).



● **FIGURE 19-12 Action of a stressor on the body.**

The stress response is a generalized pattern of reactions to any situation that threatens homeostasis.

Different stressors may produce some specific responses characteristic of that stressor; for example, the body's specific response to cold exposure is shivering and skin vasoconstriction, whereas the specific response to bacterial invasion includes increased phagocytic activity and antibody production. In addition to their specific response, however, all stressors produce a similar nonspecific, generalized response (● Figure 19-12). This set of responses common to all noxious stimuli is called the **general adaptation syndrome.** When a stressor is recognized, both nervous and hormonal responses bring about defensive measures to cope with the emergency. The result is a state of intense readiness and mobilization of biochemical resources.

To appreciate the value of the multifaceted stress response, imagine a primitive cave dweller who has just seen a large wild beast lurking in the shadows. We will consider both the neural and hormonal responses that would take place in this scenario. The body responds in the same way to modern-day stressors. You are already familiar with all these responses. At this time we are just examining how these responses work together.

ROLES OF THE SYMPATHETIC NERVOUS SYSTEM AND EPINEPHRINE IN STRESS The major neural response to such a stressful stimulus is generalized activation of the sympathetic nervous system. The resultant increase in cardiac output and ventilation as well as the diversion of blood from vasoconstricted regions of suppressed activity, such as the digestive tract and kidneys, to the more active vasodilated skeletal muscles and heart prepare the body for a fight-or-flight response. Simultaneously, the sympathetic system calls forth hormonal reinforcements in the form of a massive outpouring of epinephrine from the adrenal medulla. Epinephrine strengthens sympathetic responses and reaches places not innervated by the sympathetic system to perform additional functions, such as mobilizing carbohydrate and fat stores.

ROLES OF THE CRH–ACTH–CORTISOL SYSTEM IN STRESS Besides epinephrine, a number of other hormones are involved in

TABLE 19-2 Major Hormonal Changes during the Stress Response

Hormone	Change	Purpose Served
Epinephrine	↑	Reinforces the sympathetic nervous system to prepare the body for "fight or flight" Mobilizes carbohydrate and fat energy stores; increases blood glucose and blood fatty acids
CRH–ACTH–Cortisol	↑	Mobilizes energy stores and metabolic building blocks for use as needed; increases blood glucose, blood amino acids, and blood fatty acids ACTH facilitates learning and behavior
Glucagon	↑	Act in concert to increase blood glucose and blood fatty acids
Insulin	↓	
Renin–Angiotensin–Aldosterone; Vasopressin	↑	Conserve salt and H_2O to expand the plasma volume; help sustain blood pressure when acute loss of plasma volume occurs Angiotensin II and vasopressin cause arteriolar vasoconstriction to increase blood pressure Vasopressin facilitates learning

the overall stress response (▲ Table 19-2). The predominant hormonal response is activation of the CRH–ACTH–cortisol system. Recall that cortisol's role in helping the body cope with stress is presumed to be related to its metabolic effects. Cortisol breaks down fat and protein stores while expanding carbohydrate stores and increasing the availability of blood glucose. A logical assumption is that the increased pool of glucose, amino acids, and fatty acids is available for use as needed, such as to sustain nourishment to the brain and provide building blocks for repair of damaged tissues.

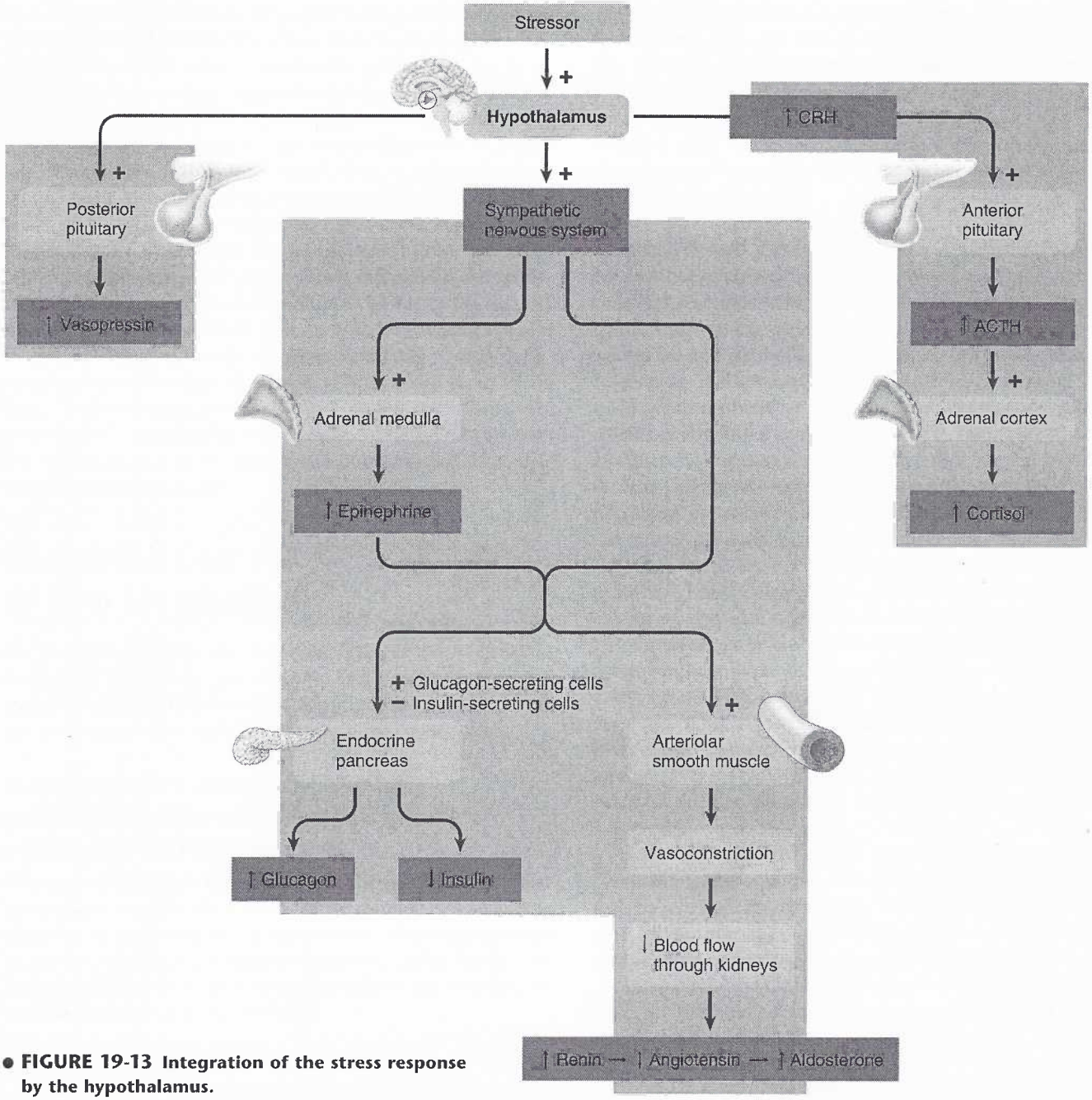
In addition to the effects of cortisol in the hypothalamus–pituitary–adrenal cortex axis, ACTH may also play a role in resisting stress. ACTH is one of several peptides that facilitate learning and behavior. Thus, an increase in ACTH during psychosocial stress may help the body cope more readily with similar stressors in the future by facilitating the learning of appropriate behavioral responses.

ROLE OF OTHER HORMONAL RESPONSES IN STRESS Besides the CRH–ACTH–cortisol system, other hormonal systems play key roles in the stress response, as follows:

- *Elevation of blood glucose and fatty acids through decreased insulin and increased glucagon.* The sympathetic nervous system and the epinephrine secreted at its bidding both inhibit insulin and stimulate glucagon. These hormonal changes act in concert to elevate blood levels of glucose and fatty acids. Epinephrine and glucagon, whose blood levels are elevated during stress, promote hepatic glycogenolysis and (along with cortisol) hepatic gluconeogenesis. However, insulin, whose secretion is suppressed during stress, opposes the breakdown of liver glycogen stores. All these effects help increase the concentration of blood glucose. The primary stimulus for insulin secretion is a rise in blood glucose; in turn, a primary effect of insulin is to lower blood glucose. If it were not for the deliberate inhibition of insulin during the stress response, the hyperglycemia caused by stress would stimulate secretion of glucose-lowering insulin. As a result, the elevation in blood glucose could not be sustained. Stress-related hormonal responses also promote a release of fatty acids from fat stores because lipolysis is favored by epinephrine, glucagon, and cortisol but opposed by insulin.
- *Maintenance of blood volume and blood pressure through increased renin–angiotensin–aldosterone and vasopressin activity.* In addition to the hormonal changes that mobilize energy stores during stress, other hormones are simultaneously called into play to sustain blood volume and blood pressure during the emergency. The sympathetic system and epinephrine play major roles in acting directly on the heart and blood vessels to improve circulatory function. In addition, RAAS is activated as a consequence of a sympathetically induced reduction of blood supply to the kidneys (see p. 527). Vasopressin secretion is also increased during stressful situations (see p. 565). Collectively, these hormones expand the plasma volume by promoting retention of salt and H_2O. Presumably, the enlarged plasma volume serves as a protective measure to help sustain blood pressure should acute loss of plasma fluid occur through hemorrhage or heavy sweating during the impending period of danger. Vasopressin and angiotensin also have direct vasopressor effects, which would be of benefit in maintaining an adequate arterial pressure in the event of acute blood loss (see p. 359). Vasopressin is further believed to facilitate learning, which has implications for future adaptation to stress.

The multifaceted stress response is coordinated by the hypothalamus.

All the individual responses to stress just described are either directly or indirectly influenced by the hypothalamus (● Figure 19-13). The hypothalamus receives input concerning physical



● **FIGURE 19-13 Integration of the stress response by the hypothalamus.**

and emotional stressors from virtually all areas of the brain and from many receptors throughout the body. In response, the hypothalamus directly activates the sympathetic nervous system, secretes CRH to stimulate ACTH and cortisol release, and triggers the release of vasopressin. Sympathetic stimulation, in turn, brings about the secretion of epinephrine, with which it has a conjoined effect on the pancreatic secretion of insulin and glucagon. Furthermore, vasoconstriction of the renal afferent arterioles by the catecholamines indirectly triggers the secretion of renin by reducing the flow of oxygenated blood through the kidneys. Renin, in turn, sets in motion RAAS. In this way, the hypothalamus integrates the responses of both the sympathetic nervous system and the endocrine system during stress.

Activation of the stress response by chronic psychosocial stressors may be harmful.

Acceleration of cardiovascular and respiratory activity, retention of salt and H_2O, and mobilization of metabolic fuels and building blocks can be of benefit in response to a physical stressor, such as an athletic competition. Most of the stressors in our everyday lives are psychosocial in nature; however, they induce these same magnified responses. Stressors such as anxiety about an exam, conflicts with loved ones, or impatience while sitting in a traffic jam can elicit a stress response. Although the rapid mobilization of body resources is appropriate in the face of real or threatened physical injury, it is generally inappropriate in re-

sponse to nonphysical stress. If no extra energy is demanded, no tissue is damaged, and no blood lost, body stores are being broken down and fluid retained needlessly, probably to the detriment of the emotionally stressed individual. In fact, there is strong circumstantial evidence for a link between chronic exposure to psychosocial stressors and the development of pathological conditions such as high blood pressure, although no definitive cause-and-effect relationship has been ascertained. As a result of "unused" stress responses, could hypertension result from too much sympathetic vasoconstriction? From too much salt and H_2O retention? From too much vasopressin and angiotensin pressor activity? A combination of these? Other factors? Recall that hypertension can develop with prolonged exposure to pharmacological levels of glucocorticoids. Could long-standing lesser elevations of cortisol, such as might occur in the face of continual psychosocial stressors, do the same thing, only more slowly? Considerable work remains to be done to evaluate the contributions that the stressors in our everyday lives make toward disease production.

Endocrine Control of Fuel Metabolism

We have just discussed the metabolic changes that are elicited during the stress response. Now we will concentrate on the metabolic patterns that occur in the absence of stress, including the hormonal factors that govern this normal metabolism.

Fuel metabolism includes anabolism, catabolism, and interconversions among energy-rich organic molecules.

The term **metabolism** refers to all the chemical reactions that occur within the cells of the body. Those reactions involving the degradation, synthesis, and transformation of the three classes of energy-rich organic molecules—protein, carbohydrate, and fat—are collectively known as **intermediary metabolism,** or **fuel metabolism** (▲ Table 19-3).

During the process of digestion, large nutrient molecules (**macromolecules**) are broken down into their smaller absorbable subunits as follows: Proteins are converted into amino acids, complex carbohydrates into monosaccharides (mainly glucose), and triglycerides (dietary fats) into monoglycerides and free fatty acids. These absorbable units are transferred from the digestive tract lumen into the blood, either directly or by way of the lymph (Chapter 16).

ANABOLISM AND CATABOLISM These organic molecules are constantly exchanged between the blood and body cells. The chemical reactions in which the organic molecules participate within the cells are categorized into two metabolic processes: anabolism and catabolism (● Figure 19-14). **Anabolism** is the buildup or synthesis of larger organic macromolecules from small organic molecular subunits. Anabolic reactions generally require energy input in the form of ATP. These reactions result in either (1) the manufacture of materials needed by the cell, such as cellular structural proteins or secretory products; or (2) storage of excess ingested nutrients not immediately needed for energy production or needed as cellular building blocks. Storage is in the form of glycogen (the storage form of glucose) or fat reservoirs. **Catabolism** is the breakdown, or degradation, of large, energy-rich organic molecules within cells. Catabolism encompasses two levels of breakdown: (1) hydrolysis (see p. 29) of large cellular organic macromolecules into their smaller subunits, similar to the process of digestion except that the reactions take place within the body cells instead of within the digestive tract lumen (for example, release of glucose by the catabolism of stored glycogen); and (2) oxidation of the smaller subunits, such as glucose, to yield energy for ATP production (see p. 37).

As an alternative to energy production, the smaller, multipotential organic subunits derived from intracellular hydrolysis may be released into the blood. These mobilized glucose, fatty acid, and amino acid molecules can then be used as needed for energy production or cellular synthesis elsewhere in the body.

In an adult, the rates of anabolism and catabolism are generally in balance, so the adult body remains in a dynamic

▲ TABLE 19-3 Summary of Reactions in Fuel Metabolism

Metabolic Process	Reaction	Consequence
Glycogenesis	Glucose → glycogen	↓ Blood glucose
Glycogenolysis	Glycogen → glucose	↑ Blood glucose
Gluconeogenesis	Amino acids → glucose	↑ Blood glucose
Protein Synthesis	Amino acids → protein	↓ Blood amino acids
Protein Degradation	Protein → amino acids	↑ Blood amino acids
Fat Synthesis (Lipogenesis or Triglyceride Synthesis)	Fatty acids and glycerol → triglycerides	↓ Blood fatty acids
Fat Breakdown (Lipolysis or Triglyceride Degradation)	Triglycerides → fatty acids and glycerol	↑ Blood fatty acids